acid carbamate (ester). It is so purified and dried that:

(i) Its cefoxitin content is not less than 850 micrograms and not more than 1,000 micrograms of cefoxitin per milligram.

(ii) Its moisture content is not more than 2.0 percent.

(iii) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 4.2 and not more than 7.0.

(iv) It gives a positive identity test.

(v) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefoxitin content, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Cefoxitin content.* Proceed as directed in §436.347 of this chapter, preparing the working standard and sample solutions and calculating the cefoxitin content as follows:

(i) *Working standard solution.* Dissolve an accurately weighed portion of the cefoxitin working standard with water to obtain a solution containing 1 milligram of cefoxitin per milliliter.

(ii) *Sample solution.* Dissolve an accurately weighed portion of the sample with water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated).

(iii) *Calculations.* Calculate the micrograms of cefoxitin per milligram of sample as follows:

$$\text{Micrograms of cefoxitin per milligram} = \frac{A_u \times P_s}{A_s \times C_u}$$

where:

A_u=Area of the cefoxitin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefoxitin peak in the chromatogram of the cefoxitin working standard;

P_s=Cefoxitin activity in the cefoxitin working standard solution in micrograms per milliliter; and

C_u=Milligrams of sample per milliliter of sample solution (estimated).

(2) *Moisture.* Proceed as directed in §436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section, except add about 25 milliliters of methanol in lieu of solvent A to a dry titrating vessel and proceed as directed in titration procedure 1.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(4) *Identity.* Proceed as directed in §436.326 of this chapter.

(5) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[49 FR 47827, Dec. 7, 1984, as amended at 55 FR 11583, Mar. 29, 1990]

§442.14a Sterile cefoxitin sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefoxitin sodium is the sodium salt of 3-(hydroxymethyl)-7α-methoxy-8-oxo-7-[2-(2-thienyl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate (ester). It is so purified and dried that:

(i) Its potency is not less than 850 micrograms and not more than 1,000 micrograms of cefoxitin per milligram. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefoxitin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 2.0 percent.

(vi) Its pH in an aqueous solution is not less than 4.2 and not more than 7.0.

(vii) It gives a positive identity test.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, identity, and crystallinity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 1 gram.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.347 of this chapter, preparing the working standard and sample solutions and calculating the cefoxitin content as follows:

(i) *Working standard solution*. Dissolve an accurately weighed portion of the cefoxitin working standard with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter.

(ii) *Sample solutions.* Dissolve an accurately weighed portion of the sample with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated); and also if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to obtain a solution containing 1 milligram of cefoxitin per milliliter (estimated).

(iii) *Calculations*—(*a*) Calculate the cefoxitin content in micrograms per milligram as follows:

$$\text{Micrograms of cefoxitin per milligram} = \frac{A_u \times P_s}{A_s \times C_u}$$

where:

A_u=Area of the cefoxitin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefoxitin peak in the chromatogram of the cefoxitin working standard;

P_s=Cefoxitin activity in the cefoxitin working standard solution in micrograms per milliliter; and

C_u=Milligrams of sample per milliliter of sample solution (estimated).

(*b*) Calculate the cefoxitin content of the vial as follows:

$$\text{Milligrams of cefoxitin per vial} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_u=Area of the cefoxitin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefoxitin peak in the chromatogram of the cefoxitin working standard;

P_s=Cefoxitin activity in the cefoxitin working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 50 milligrams of cefoxitin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section, except add about 25 milliliters of methanol in lieu of solvent A to a dry titrating vessel and proceed as directed in titration procedure 1.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(7) *Identity*. Proceed as directed in § 436.326 of this chapter, preparing the sample as follows: Prepare a solution containing about 2.5 milligrams of cefoxitin per milliliter in distilled water.

(8) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[44 FR 10374, Feb. 20, 1979, as amended at 50 FR 19919, May 13, 1985; 51 FR 27532, Aug. 1, 1986]

§442.15 Cefixime trihydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefixime trihydrate is the trihydrate form of [6*R*-[6 α, 7B(*Z*)]]-7-[[(2-amino-4-thiazolyl) [(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 950 micrograms and not more than 1,030 micrograms of cefixime activity per milligram, on an anhydrous basis.

(ii) Its moisture content is not less than 9.0 percent and not more than 12.0 percent.

(iii) The pH of an aqueous solution containing the equivalent of 0.7 milligram per milliliter is not less than 2.6 and not more than 4.1.

(iv) It is crystalline.

(v) The specific rotation in a 2.0 percent sodium bicarbonate solution containing 10.0 milligrams of cefixime per milliliter at 25 °C is between −75° and −88° calculated on an anhydrous basis.

(vi) It gives a positive identity test for cefixime.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results for tests and assays on the batch for potency, moisture, pH, crystallinity, specific rotation, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams, and 1 package containing approximately 5 grams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.216 of this chapter, using an ultraviolet detection system operating at a wavelength of 254 nanometers, and a column (typically 3 centimeters × 4.6 millimeters) packed with a 3-micron octadecyl hydrocarbon bonded silica or equivalent at ambient temperature. Reagents, working standard, test and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(A) *Phosphoric acid solution.* Add 10 milliliters of concentrated phosphoric acid to 90 milliliters of water.

(B) *Tetrabutylammonium hydroxide solution.* Dilute 25 milliliters of 0.4*M* tetrabutylammonium hydroxide solution to 1,000 milliliters with water. Adjust the pH to 7.0 with phosphoric acid solution.

(C) *Mobile phase.* Add 775 milliliters of the tetrabutylammonium hydroxide solution to 225 milliliters of acetonitrile. Filter the mobile phase through a suitable glass filter or equivalent which is capable of removing particulate contamination greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(D) *0.1M Phosphate buffer, pH 7.0.* Add 6.8 milliliters of concentrated phosphoric acid to 300 milliliters of water. Adjust the pH to 7.0 with 10*N* sodium hydroxide. Dilute to 1,000 milliliters with water.

(ii) *Preparation of working standard, test and sample solutions*—(A) *Working standard solution.* Dissolve an accurately weighed portion of the cefixime standard with sufficient 0.1*M* phosphate buffer, pH 7.0, to obtain a solution of known concentration containing approximately 2 milligrams of cefixime activity per milliliter. Further dilute quantitatively to a final concentration of 0.2 milligram of cefixime activity per milliliter in 0.1 *M* phosphate buffer, pH 7.0. Prepare the working standard solution just prior to its introduction into the chromatograph.

(B) *System suitability test solution.* Dissolve an accurately weighed portion of cefixime working standard in distilled water to obtain a solution containing approximately 1.0 milligram of cefixime activity per milliliter. Heat this solution at 95 °C (in an oil bath) for 45 minutes. This procedure allows the (E)-isomer of cefixime to be generated *in situ.* Prepare the test solution